A Synthesis of Aaptamine from 6,7-Dimethoxy-1-methylisoquinoline

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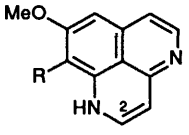
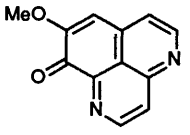
6,7-Methoxy-1-methylisoquinoline **3a** was nitrated at C-8, oxidised to the nitro aldehyde **3r** and then condensed with nitromethane using alumina as base to give the alcohol **3s**, dehydration of which produced the nitroethene **3t**. Iron–acetic acid treatment of compound **3t** produced aaptamine **1a**. Isoquinoline-1-carbaldehydes **3q** and r reacted with ammonium acetate to produce imidazo[5,1-*a*]isoquinolines **6a** and **6b**. 1-Lithiomethyl-6,7-dimethoxyisoquinoline reacted with ethyl chloroformate to give the ester **3l** which was, in turn, easily oxidised to the α-keto ester **3n**. The latter was nitrated to give **3o**, and this was reductively cyclised to afford the 1*H*-benzo[*d*,*e*][1,6]naphthyridine-2,3-dione **4**.

The bright yellow substance, aaptamine **1a**, 8,9-dimethoxy-1*H*-benzo[*d*,*e*][1,6]naphthyridine, was isolated as its protonic salt from an Okinawan sea sponge, *Aaptos aaptos*, and shown to have powerful α-adrenoceptor blocking activity.[1,2] Later, cytotoxic and antimicrobial demethylaaptamine **1b** and demethylated and oxidised variant **2** were isolated from the same natural source.[3] These three compounds represent the only reported examples of the 1*H*-benzo[d,e][1,6]naphthyridine ring system in a naturally occurring substance. It seems likely that the skeleton of these compounds is produced in nature from dihydroxyphenylalanine (DOPA) in combination with a second component, perhaps asparagine.



1
a; R = MeO
b; R = HO



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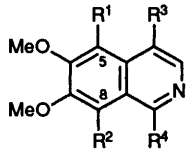
From a synthetic viewpoint the 1*H*-benzo[*d*,*e*][1,6]naphthyridine ring system can be viewed either as a quinoline or as an isoquinoline, but with an additional, fused six-membered nitrogen-containing ring. Of the six total syntheses of aaptamine previously reported,[4] three[4a,e,f] took an approach in which a quinoline was constructed first and three[4b–d] in which the third ring was fused to an existing isoquinoline. The work described here utilised the readily available[5] 6,7-dimethoxy-1-methylisoquinoline **3a** as a starting point.

Compound **3a** contains all the necessary skeletal atoms for aaptamine, except one carbon and one nitrogen. It was our plan to introduce nitrogen at C-8 before inserting the additional carbon (C-2 in **1a**). We envisaged that the acidity of hydrogens of the 1-methyl group in compound **3a** would permit the introduction of the additional carbon atom at a later stage. This plan was supported by a report[6] that side-chain lithiation of compound **3a** can be achieved with butyllithium at room temperature; the resulting 1-lithiomethyl-6,7-dimethoxyisoquinoline was trapped with a variety of electrophilic species.[6]

Nitration of isoquinoline itself occurs, *via* the *N*-protonated isoquinolinium cation,[7] at the 5- and 8-positions, with the former predominating in the ratio of 9:1.[8] It was our anticipation then that nitration of 6,7-dimethoxy-1-methylisoquinoline **3a** would favour the less hindered 5-position. Thus insertion of nitrogen, *via* a C-8 nitration, seemed to require a reversible blocking of C-5.



3	R^1	R^2	R^3	R^4		R^1	R^2	R^3	R^4
a;	H	H	H	Me	**f**;	H	NH_2	H	Me
b;	Br	H	H	Me	**g**;	H	NO_2	H	Me
c;	H	H	Br	Me	**h**;	NO_2	NO_2	H	Me
d;	Br	Br	H	Me	**i**;	H	NC	H	Me
e;	Br	NO_2	H	Me	**j**;	H	NHCHO	H	Me

	R^1	R^2	R^3	R^4
k;	H	$N(CH_2Ph)CHO$	H	Me
l;	H	H	H	CH_2CO_2Et
m;	H	H	H	$C(CO_2Et)_3$
n;	H	H	H	$COCO_2Et$
o;	H	NO_2	H	$COCO_2Et$

	R^1	R^2	R^3	R^4
p;	H	NH_2	H	CO_1CO_2Et
q;	H	H	H	CHO
r;	H	NO_2	H	CHO
s;	H	NO_2	H	$CH(OH)CH_2NO_2$
t;	H	NO_2	H	$CH{=}CHNO_2$
u;	H	NO_2	H	$CH(CH_2NO_2)CH_2NO_2$

Results

Electrophilic bromination of compound **3a** with an excess of bromine in refluxing chloroform produced mainly the predicted 5-bromoisomer **3b** together with 4-monobromo and 5,8-dibromo derivatives **3c** and **3d**, respectively. The location of the halogen in compound **3b** was established by the observation of an NOE between the 1-methyl group and the aromatic 8-hydrogen.

Nitration of compound **3b**, blocked at C-5, gave the desired 8-nitro derivative **3e**, then exposure of compound **3e** to hydrogen, firstly over platinum then separately over palladium–charcoal, allowed removal of the bromine blocking substituent while effecting reduction of the nitro group, generating 8-amino-6,7-dimethoxy-1-methylisoquinoline **3f**.

Subsequently we found that direct, low temperature nitration of the 1-methylisoquinoline **3a** leads to the 8-nitro derivative **3g**

in contrast with our prediction and with the observed regiochemistry of bromination; we have presented a rationalisation[9] for this regioselectivity. Even at −45 °C the mononitro derivative **3g** was always accompanied by some 5,8-dinitro derivative **3h**, but the desired compound **3g** could be separated easily by crystallisation.

Our initial strategy for the introduction of the C_1-unit required between the 8-nitrogen and the C-1-carbon substituents was to engineer an electrophilic carbon on an 8-nitrogen substituent for subsequent ring closure. Thus, after conversion of the amine **3f** into the isonitrile **3i** we sought to effect a cyclisation patterned on reports[10] of electronically analogous ring closures of aromatic isonitriles onto benzylic carbons to afford indoles, with lithium diisopropylamide[10a] (LDA) or copper(I) oxide,[10b] however the former gave only a multi-component mixture and the latter, even in refluxing xylene, brought no change to **3i**.

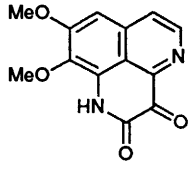
Conversion of the amine **3f** into the formamide **3j** allowed us to pursue attempts to follow another seemingly excellent precedent,[11] in which the cyclising condensation of a 5 quinolylformamide with the quinoline 4-methyl group was reported. Unfortunately, treatment of the formamide **3j** under various acidic conditions, phosphorus oxychloride, phosphorus pentoxide or toluene-*p*-sulphonic acid, led only to recovery of starting formamide. The alternative, that base-catalysed conditions, such as those used in the intermolecular condensation of *N*-methylformanilide with 4-methylpyridine using sodium hydride,[12] might allow the desired cyclising condensation, required prior removal of the acidic amide-*N*-hydrogen. The formamide was accordingly *N*-benzylated, giving compound **3k**, but even then no cyclisation could be achieved with a variety of strong bases, from sodium hydride to sodium hexamethyldisilazide.

We next turned to the option of introducing the required C_1-unit directly onto the existing carbon side chain. Attempts to bring about a condensation with dimethylformamide dimethyl acetal, intending to parallel the Leimgruber–Batcho indole synthesis[13] in a six-membered sense, were fruitless, no reaction taking place.

Addition of a solution of 1-lithiomethyl-6,7-dimethoxyisoquinoline[6] to ethyl chloroformate produced the expected alkylation product **3l** together with the product of further alkylation, the triester **3m**. The ester **3l** was susceptible to easy aerial oxidation, generating the oxo ester **3n**, also available *via* selenium dioxide treatment of **3l**.

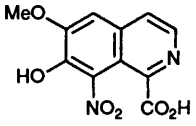
Attempted low temperature nitration of the ester **3l** was unpromising, a multicomponent mixture resulting. However, comparable treatment of the α-keto ester **3n** proceeded cleanly to the 8-nitro derivative **3o**, the regiochemistry of substitution being confirmed by the observation of an NOE effect between C-4 and C-5 protons.

Various reductive conditions were applied to the keto ester **3o**, the most productive of which was the use of platinum oxide with hydrogen at atmospheric pressure. From this there was obtained the tricyclic keto amide **4** together with a trace of the bicyclic amino ester **3p**, though neither in good yield. Although product **4** contains the aaptamine skeleton, modification of the oxidation level of the newly formed ring and the production therefrom of aaptamine was not pursued in the light of the poor yield in the reductive cyclisation and the development of a preferable and successful alternative route.



4

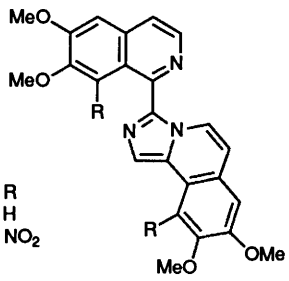
The nitroisoquinoline **3g** was converted by oxidation with selenium dioxide into the aldehyde **3r**. It was found to be critical to exclude water – for example the reaction time was six times longer if dioxane containing only 0.5% water was used. The relative molar quantity of oxidant and substrate was also found to be important: with 1 mol equiv. a mixture of starting material and product aldehyde was always obtained, however, using 1.5 mol equiv. complete consumption of starting material occurred within 2.5 h in refluxing dry dioxane, though these conditions also led to the formation of some phenolic acid **5** as by-product. Demethylation of the 7-methoxy was confirmed by the observation of an NOE effect between the remaining 6-methoxy and the 5-hydrogen.



5

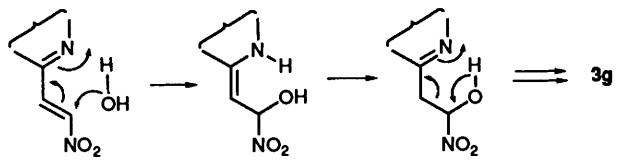
With the aldehyde **3r** in hand, attention could now turn to the possibility of effecting a condensation with nitromethane, the goal being the nitroalkene **3t** having both the required extra carbon and functionality to allow cyclisation.

Considerable difficulties were encountered in evolving suitable conditions for the condensation. One set of conditions, ammonium acetate in acetic acid, led to the unexpected, and apparently unprecedented, formation of imidazo[5,1-*a*]isoquinoline **6b** in high yield. A comparable product **6a** was formed using the aldehyde **3q**.



6 R
a; H
b; NO_2

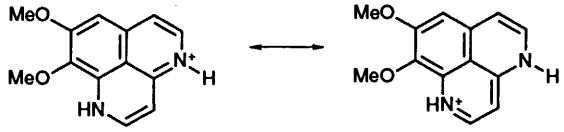
The desired condensation of the aldehyde **3r** and nitromethane could be effected with butyllithium in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) producing some of the desired alcohol **3s**, but it took a great deal of experimentation to improve on the 15% yield. Attempts to use sodium methoxide, potassium t-butoxide, triethylamine, diisopropylamine in varying quantities, solvents, hot and cold were all unsuccessful. The key observation came from an examination of the use of basic alumina which in 50-fold excess and in nitromethane as solvent gave the trinitro compound **3u**. This was taken to mean that the required condensation had indeed taken place, and that dehydration had followed to generate the target nitroalkene **3t**, which, under the conditions of reaction, had undergone the Michael addition of a second mole equivalent of nitromethane anion. Further experimentation allowed efficient and clean synthesis of the alcohol **3s** by controlling the ratio of alumina to nitromethane (as solvent and reactant); at least eight equivalents of alumina was required for the successful room temperature condensation to produce **3s**. In addition to the alcohol, a small amount of methylnitroisoquinoline **3g** was obtained by chromatography. This latter must derive from the



nitroalkene *via* hydration to a species (part structure **7**) which then loses the elements of nitroformaldehyde (arrows on **7**).

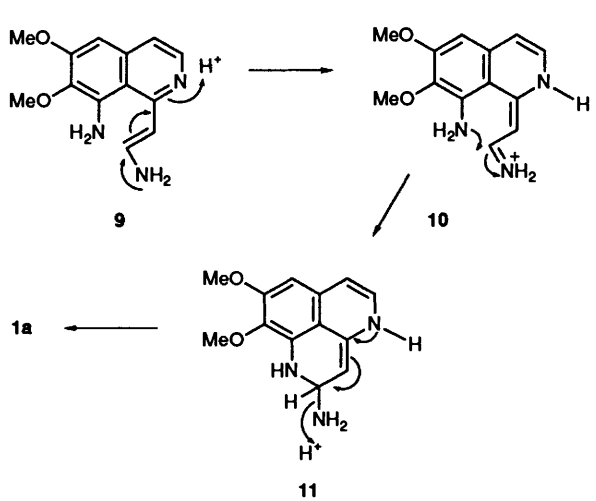
Dehydration of the alcohol also proved to be more difficult than we had expected: a variety of acidic conditions failed, probably because of interaction of the isoquinoline nitrogen with proton/acid. The production of Michael adduct **3u** (above) prompted an investigation into the use of non-acidic and base-catalysed dehydration; many conditions were assessed, including Florisil and molecular sieves; the best found, refluxing benzene containing alumina, gave the desired nitroalkene **3t** (36%), together with aldehyde **3r** (19%), from the reverse of the condensation by which it was produced and trinitro compound **3u** (7%).

Finally, the ring closure of nitro alkene **3t** was modelled on the frequently used cyclisation of 2-(2-nitrophenyl)-1-nitroethenes to produce the five-membered ring of indoles.[14] Such indole ring syntheses would generally be thought to derive benefit from the final formation of the aromatic pyrrole ring. In the present context we viewed the final formation of the pyridinium ring (resonance contributor **8**) as likely to be of assistance.



One may view the desired process as needing reduction of both nitro groups to generate **9**, or its equivalent, for enamine protonation, cyclisation and loss of ammonia, generating the aaptamine system. Mildly acidic conditions in the reduction–cyclisation would facilitate the step proceeding from conjugated enamine **9** to **10**, and, in the final elimination (arrows on **11**), and by protonating the amino group, allow loss of ammonia producing aaptamine, as its protonic salt.

Attempts to utilise catalytic hydrogen transfer conditions,[15] titanium trichloride in aqueous hydrochloric acid or iron with hydrochloric acid were unsuccessful, however, the use of iron



powder in acetic acid[16] allowed conversion of nitroalkene **3t** into aaptamine hydrochloride in 83% yield, the synthetic material having a melting point and spectroscopic properties identical with those reported.[1] We found that liberation of the free base of aaptamine produced material which is very easily aerially oxidised; the initially yellow material blackening within 10 to 15 min, but it can be stored and handled in solution especially as its hydrochloride salt.

Experimental

6,7-Dimethoxy-1-methylisoquinoline **3a**.—This was prepared (98%) according to the literature procedure[5] with the modification that the dehydrogenation was conducted (10 h) with 5% palladium–charcoal in refluxing substrate, *i.e.* 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline.

5-Bromo-6,7-dimethoxy-1-methylisoquinoline **3b**, *4-Bromo-6,7-dimethoxy-1-methylisoquinoline* **3c** *and 4,5,8-Tribromo-6,7-dimethoxy-1-methylisoquinoline* **3d**.—The isoquinoline **3a** (631 mg) and bromine (4.78 g) were heated together, in the absence of light, at reflux in dry ethanol-free chloroform (20 ml) for 24 h. The resulting solution was cooled, washed with aqueous sodium thiosulphate, dried and evaporated to leave a brown gum (955 mg), from which, by chromatography over silica, using a solvent gradient of toluene, ethyl acetate and methanol, there were obtained, in order of elution, *tribromoisoquinoline* **3d** (89 mg) as a gum, δ_H($CDCl_3$; 60 MHz) 2.35 (3 H, s, 1-CH_3), 4.05 (3 H, s, OCH_3), 4.10 (3 H, s, OCH_3), 7.25 (1 H, s, 3-H); *m/z* (EI) 443, 441, 439, 437 ($M^{\cdot+}$, 3, 10, 9, 3%), 363 (48), 362 (50), 361 (100), 360 (69), 359 (54), 358 (35), 318 (15) and 316 (11); (Found: 438.8234. $C_{12}H_{10}Br_3NO_2$ requires 438.8243).

4-Bromoisoquinoline **3c** (110 mg), m.p. 162–164 °C (from petroleum ether), λ_{max}/nm(EtOH) 243, 248sh, 285, 315 and 330 (log ε 4.8, 4.78, 4.04, 3.9 and 3.89); δ_H[$(CD_3)_2CO$; 220 MHz)] 2.8 (3 H, s, 1-CH_3), 4.05 (6 H, s, 2 × OCH_3), 7.4 (1 H, s, 5-H), 7.48 (1 H, s, 8-H) and 8.4 (1 H, s, 3-H); *m/z* (EI) 283, 281 ($M^{\cdot+}$, 100, 98%), 284, 282 (58, 64), 268, 266 (10, 10), 240, 238 (33, 37), 197, 195 (13, 12), 184 (20), 159 (53) and 157 (11) (Found: C, 51.0; H, 4.3; Br, 28.3; N, 4.6. $C_{12}H_{12}BrNO_2$ requires C, 51.1; H, 4.3; Br, 28.3; N, 4.9%).

Lastly *5-bromoisoquinoline* **3b** (550 mg, 63%), m.p. 109–110 °C [from light petroleum (b.p. 60–80 °C)], λ_{max}/nm(EtOH) 239, 270sh, 280sh, 325 and 328 (log ε 4.44, 3.52, 3.52, 3.37 and 3.41); δ_H($CDCl_3$; 300 MHz) 2.94 (3 H, s, 1-CH_3), 4.0 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 7.38 (1 H, s, 8-H), 7.84 (1 H, d, *J* 6 Hz, 3-H) and 8.44 (1 H, d, *J* 6 Hz, 4-H); *m/z* (EI) 283, 281 ($M^{\cdot+}$, 97, 100%), 284, 282 (13, 15), 240, 238 (20, 23), 187 (27) and 159 (11) (Found: C, 50.9; H, 4.2; N, 4.5; Br, 28.4. $C_{12}H_{12}BrNO_2$ requires C, 51.0; H, 4.3; N, 4.9; Br, 28.3%).

5-Bromo-6,7-dimethoxy-1-methyl-8-nitroisoquinoline **3e**.—The 5-bromoisoquinoline **3b** (1.07 g) was nitrated with fuming nitric acid (40 ml) between −50 and −40 °C for 0.5 h. The mixture was added to ice, made basic with potassium carbonate and product extracted with ethyl acetate to give the *bromonitroisoquinoline* **3e** (0.85 g, 68%) as a yellow crystalline solid, m.p. 128–131 °C (from ethanol), λ_{max}/nm(EtOH) 232, 283 and 330 (log ε 4.06, 3.3 and 3.09); δ_H($CDCl_3$; 300 MHz) 2.82 (3 H, s, 1-CH_3), 4.04 (6 H, s, 2 × OCH_3), 8.01 (1 H, d, *J* 6 Hz, 4-H) and 8.56 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 328, 326 ($M^{\cdot+}$, 98, 100%), 311, 309 (80, 82), 267, 265 (25, 25) and 252, 250 (18, 18) (Found: C, 43.4; H, 3.35; N, 8.4; Br, 24.9. $C_{12}H_{11}BrN_2O_4$ requires C, 44.0; H, 3.39; N, 8.5; Br, 24.4%).

6,7-Dimethoxy-1-methyl-8-nitroisoquinoline **3g** *and 6,7-Dimethoxy-5,8-dinitro-1-methylisoquinoline* **3h**.—The isoquinoline **3a** (15 g) was added portionwise during 45 min to stirred fuming

nitric acid (150 ml) at such a rate as to maintain the temperature between −40 and −45 °C. Stirring was continued for a further 45 min. The mixture was poured into ice water, made basic with solid sodium bicarbonate and extracted with ethyl acetate. The dried organic extract was evaporated and the residue crystallised from 95% ethanol to give 8-*nitroisoquinoline* **3g** (5.2 g). From the mother liquor, by crystallisation successively from toluene–light petroleum (b.p. 60–80 °C) then 95% ethanol, further **3g** (0.75 g) could be obtained. Chromatography of all combined mother liquor material (6.31 g) over silica, eluting with a gradient of hexane and acetone, gave a fraction (3.4 g) which was crystallised from methanol then from 95% ethanol to produce more **3g** (0.7 g). The total yield of pure **3g** was 7.55 g (41%), m.p. 185–186 °C, $\delta_H(CDCl_3$; 300 MHz) 2.66 (3 H, s, 1-CH_3), 3.90 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 7.07 (1 H, s, 5-H), 7.29 (1 H, d, *J* 5.7 Hz, 4-H) and 8.22 (1 H, d, *J* 5.7 Hz, 3-H); *m/z* (EI) 248 ($M^{\cdot+}$, 100), 231 (71), 115 (32), 91 (50) and 71 (71) (Found: 248.0792. $C_{12}H_{12}N_2O_4$ requires 248.0797). Chromatography of mother liquors produced the 6,7-dimethoxy-5,8-dinitro-1-methylisoquinoline, which could be made the only product (65%) by nitration with concentrated nitric acid–concentrated sulphuric acid (1:1) at 0 °C for 3 h, m.p. 142–144 °C.

8-*Amino*-6,7-*dimethoxy*-1-*methylisoquinoline* **3f**.—(*a*) The bromonitroisoquinoline **3e** (9 mg) was hydrogenated over platinum (10 mg) in ethanol (5 ml) at 60 psi for 16 h. The solution was filtered through Celite, 5% palladium–charcoal (20 mg) was added and a further hydrogenation conducted under the same conditions for 48 h. Filtration and evaporation gave the *aminoisoquinoline* **3f** (5.5 mg, 86%), as a yellow gum, λ_{max}/nm(EtOH) 248 and 335 (log ε 4.18 and 2.92); ν_{max}/cm^{-1}(film) 3340; $\delta_H(CDCl_3$; 60 MHz) 3.1 (3 H, s, 1-CH_3), 3.84 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 4.78 (2 H, s, NH_2), 6.56 (1 H, s, 5-H), 7.18 (1 H, d, *J* 6 Hz, 4-H) and 8.12 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 218 ($M^{\cdot+}$, 80%), 203 (100), 163 (14) and 160 (17).

(*b*) To nitroisoquinoline **3g** (40 mg) in methanol (10 ml) at −5 °C was added palladium(II) chloride (84 mg) then sodium borohydride (60 mg) in portions during 0.5 h. Filtration through Celite, evaporation of the filtrate and partitioning of the resultant residue between water and ethyl acetate gave, from the organic layer, the pure amine **3f** (35 mg, 87%) identical with that obtained in (*a*) above.

(*c*) To a solution of nitroisoquinoline **3g** (381 mg) in dry methanol (30 ml) under nitrogen was added palladium–charcoal (10%, 208 mg) and ammonium formate (1.12 g), and the mixture refluxed with vigorous stirring for 2 h. Filtration through Celite and evaporation gave a brown gum to which aqueous potassium carbonate was added and product isolated by extraction with chloroform to give the amine **3f** (278 mg, 83%), identical with material from (*a*) and (*b*) in spectroscopic properties, but crystalline, m.p. 149–151 °C (from dichloromethane–diethyl ether) (Found: C, 65.8; H, 6.6; N, 12.5. $C_{12}H_{12}N_2O_2$ requires C, 66.0; H, 6.5; N, 12.8%).

6,7-*Dimethoxy*-1-*methyl*-8-*isoquinolyl Isocyanide* **3i**.—The aminoisoquinoline **3f** (67 mg) in dichloromethane (20 ml) under nitrogen was treated with aqueous sodium hydroxide (50%; 20 ml) and tetrabutylammonium hydroxide (0.5 g) and the whole was vigorously stirred while chloroform (38 mg) was added dropwise over 3 h. After 12 h, the organic layer was separated, dried and evaporated to leave a black gum from which the *isocyanide* **3i** (22 mg, 31%) was obtained by flash chromatography over silica, m.p. 180–184 °C (from methanol), λ_{max}/nm(EtOH) 240, 278sh, 291, 303 and 327 (log ε 3.92, 3.15, 3.15, 3.16 and 2.93); ν_{max}/cm^{-1}(film) 2140; $\delta_H[(CD_3)_2CO$; 300 MHz] 3.2 (3 H, s, 1-CH_3), 4.1 (3 H, s, OCH_3), 4.15 (3 H, s, OCH_3), 7.63 (1 H, s, 5-H), 7.66 (1 H, d, *J* 6 Hz, 4-H) and 8.38 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 228 ($M^{\cdot+}$, 100%), 227 (20), 213 (16), 199 (12), 185 (23), 184 (14), 170 (23), 168 (13), 155 (13), 142 (20), 115 (11) (Found: C, 67.6; H, 5.2; N, 11.9. $C_{13}H_{12}N_2O_2$ requires C, 67.8; H, 5.2; N, 12.2%).

6,7-*Dimethoxy*-8-*formamido*-1-*methylisoquinoline* **3j**.—To the amine **3f** (191 mg) in formic acid (10 ml; 90%) at −10 °C was added acetic anhydride (8 ml). The mixture was brought to room temperature during 1 h, then quenched with ice. The mixture was made basic with potassium carbonate and organic material extracted into ethyl acetate, drying ($MgSO_4$) and evaporation of which gave the *formamide* **3j** (193 mg, 89%) as colourless crystals, m.p. 200–204 °C (from aqueous methanol), λ_{max}/nm)EtOH) 237, 283 and 321 (log ε 3.8, 3.3 and 3.0); ν_{max}/cm^{-1}(film) 3400 and 1700; $\delta_H[(CD_3)_2SO$; 300 MHz] 2.84 (0.66 × 3 H, s, 1-CH_3), 2.91 (0.33 × 3 H, s, 1-CH_3), 3.72 (0.33 × 3 H, s, OCH_3), 3.74 (0.66 × 3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 7.44 (1 H, s, 5-H), 7.57 (1 H, d, *J* 6 Hz, 4-H), 8.09 (0.33 H, d, *J* 12 Hz, CHO), 8.2 (1 H, d, *J* 6 Hz, 3-H), 8.44 (0.66 H, d, *J* 12 Hz, CHO), 9.64 (0.33 H, d, *J* 12 Hz, NH) and 9.92 (0.66 H, d, *J* 12 Hz, NH); *m/z* (EI) 246 ($M^{\cdot+}$, 31%), 231 (10) and 203 (30) (Found: C, 62.4; H, 5.7; N, 10.9. $C_{13}H_{14}N_2O_3$. 0.3 H_2O requires C, 62.0; H, 5.7; N, 11.1%).

8-N-*Benzylformamido*-6,7-*dimethoxy*-1-*methylisoquinoline* **3k**.—To a slurry of formamide **3j** (98 mg) and sodium hydride (23 mg) in dry tetrahydrofuran (THF) (20 ml) under nitrogen at room temperature was added benzyl bromide (79 mg) then the mixture was refluxed for 3 h. Addition to ice and extraction with ethyl acetate produced the *N*-benzylformamide (88 mg, 58%), as off-white crystals, m.p. 135–138 °C (from aqueous ethanol), λ_{max}/nm(EtOH) 239, 289 and 330sh (log ε 4.35, 3.33 and 3.13); ν_{max}/cm^{-1}(film) 1670; $\delta_H(CDCl_3)$ 2.78 (0.2 × 3 H, s, 1-CH_3), 2.84 (0.8 × 3 H, s, 1-CH_3), 3.12 (0.8 × 3 H, s, OCH_3), 3.70 (0.2 × 3 H, s, OCH_3), 3.94 (0.8 × 3 H, s, OCH_3), 3.99 (0.2 × 3 H, s, OCH_3), 4.08 (0.8 H, d, *J* 12 Hz, $PhCH_2$), 4.59 (0.2 H, d, *J* 12 Hz, $PhCH_2$), 4.84 (0.2 H, d, *J* 12 Hz, $PhCH_2$), 5.54 (0.8 H, d, *J* 12 Hz, $PhCH_2$), 7.7–7.3 (6 H, m, ArH), 7.42 (1 H, d, *J* 6 Hz, 4-H), 8.36 (1 H, s, CHO) and 8.40 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 336 ($M^{\cdot+}$, 32%), 219 (11), 203 (10) and 91 (100) (Found: C, 71.4; H, 5.9; N, 7.9. $C_{20}H_{20}N_2O_3$ requires C, 71.4; H, 6.0; N, 8.3%).

Ethyl 6,7-*Dimethoxyisoquinolin*-1-*ylacetate* **3l** *and Triethyl* 6,7-*Dimethoxyisoquinolin*-1-*ylmethanetricarboxylate* **3m**.—To a solution of the isoquinoline **3a** in dry THF (25 ml) under nitrogen was added butyllithium (1.65 mol dm^{-3} in hexane, 1.75 ml) and the solution stirred at room temperature for 0.5 h. The resulting solution was added dropwise during 0.5 h to ethyl chloroformate (2.27 g) in THF (20 ml). The mixture was stirred for a further 2 h, added to water and the organic material extracted into ethyl acetate. Evaporation of the dried extract produced a red gum (595 mg) from which, by chromatography over silica and eluting with ethyl acetate there was obtained *ester* **3l** (154 mg, 21%) as a yellow oil, λ_{max}/nm(EtOH) 233, 313 and 326; ν_{max}/cm^{-1}(film) 1730; $\delta_H(CDCl_3$; 60 MHz) 1.1 (3 H, t, *J* 6 Hz, OCH_2CH_3), 3.9–4.25 (10 H, m, CH_2, OCH_2CH_3, OCH_3), 6.95 (1 H, s, 5-H), 7.2 (1 H, s, 8-H), 7.3 (1 H, d, *J* 6 Hz, 4-H) and 8.2 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 275 ($M^{\cdot+}$, 35%), 229 (14), 204 (14), 203 (100), 202 (55), 188 (18), 172 (11), 171 (27) and 115 (10) (Found: 275.1162. $C_{15}H_{17}NO_4$ requires 275.1157).

Also *triester* **3m** (108 mg, 10%) as colourless crystals, m.p. 141–142 °C (from 95% ethanol), λ_{max}/nm(EtOH) 232, 268, 312 and 325 (log ε 4.04, 3.54, 3.56 and 3.64); ν_{max}/cm^{-1}(film) 1740 and 1730; $\delta_H(CDCl_3$; 60 MHz) 1.2 (9 H, t, *J* 7 Hz, OCH_2CH_3), 3.8 (3 H, s, OCH_3), 3.9 (3 H, s, OCH_3), 4.25 (6 H, q, *J* 7 Hz, OCH_2CH_3), 6.9 (1 H, s, 5-H), 6.95 (1 H, s, 8-H), 7.35 (1 H, d, *J* 6 Hz, 4-H) and 8.15 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 419 ($M^{\cdot+}$, 35%),

301 (15), 275 (18), 232 (12), 229 (38), 203 (20) and 188 (50) (Found: C, 60.2; H, 6.1; N, 3.1. $C_{21}H_{25}NO_8$ requires C, 60.1; H, 6.0; N, 3.3%).

Ethyl 6,7-*Dimethoxyisoquinolin*-1-*ylglyoxylate* **3n**.—The ester **3l** (256 mg) was oxidised with selenium dioxide (124 mg) in refluxing dry dioxane (20 ml) for 1 h. Filtration and evaporation of the dioxane left a red, semicrystalline solid (294 mg) from which, by treatment of a hot methanolic solution with charcoal, there was obtained the *glyoxylate* **3n** (240 mg, 89%) as yellow crystals, m.p. 178–180 °C (from methanol), λ_{max}/nm(EtOH) 236, 260, 328 and 360 (log ε 4.71, 4.21, 3.60 and 3.65); ν_{max}/cm^{-1}(film) 1740 and 1695; δ_H($CDCl_3$; 300 MHz) 1.3 (3 H, t, *J* 6 Hz, OCH_2CH_3), 4.0 (6 H, s, 2 × OCH_3), 4.45 (2 H, q, *J* 6 Hz, OCH_2CH_3), 7.05 (1 H, s, 5-H), 7.65 (1 H, d, *J* 6 Hz, 4-H) and 8.45 (1 H, d, *J* 6 Hz, 8-H); *m/z* (EI) 289 ($M^{\cdot+}$, 4%), 216 (22), 189 (23) and 188 (100) (Found: C, 59.7; H, 5.2; N, 4.6. $C_{15}H_{13}NO_5$ requires C, 59.4; H, 5.4; N, 4.4%).

Ethyl 6,7-*Dimethoxy*-8-*nitroisoquinolin*-1-*ylglyoxylate* **3o**.—The glyoxylate **3n** (121 mg) was nitrated with fuming nitric acid (6 ml) at −40 °C for 2.5 h. The reaction solution was poured onto ice, sodium hydrogen carbonate was added and organic material was extracted with ethyl acetate to provide the *nitroglyoxylate* **3n** (80 mg, 57%) as colourless crystals, m.p. 123–125 °C, λ_{max}/nm(EtOH) 228, 245 and 328 (log ε 4.38, 4.37 and 3.76); ν_{max}/cm^{-1}(film) 1730 and 1715; δ_H($CDCl_3$; 300 MHz) 1.43 (3 H, t, *J* 6 Hz, OCH_2CH_3), 4.12 (6 H, s, 2 × OCH_3), 4.57 (2 H, q, OCH_2CH_3), 7.36 (1 H, s, 5-H), 7.78 (1 H, d, 4-H) and 8.63 (1 H, d, *J* 6 Hz, 3-H); *m/z* (CI) 335 (MH^+, 80%), 290 (14), 189 (14), 288 (23), 287 (43), 277 (12), 260 (15), 259 (24), 232 (28), 231 (100) and 230 (12) (Found: C, 53.9; H, 4.4; N, 8.0. $C_{15}H_{14}N_2O_7$ requires C, 53.9; H, 4.2; N, 8.4%).

Ethyl 8-*Amino*-6,7-*dimethoxyisoquinolin*-1-*ylglyoxylate* **3p** *and* 2,3-*dihydro*-8,9-*dimethoxy*-1H-*benzo*[d,e][1,6]*naphthyridine*-2,3-*dione* **4**.—Treatment of the nitroglyoxylate **3o** (0.90 g) with hydrogen at atmospheric pressure and room temperature over platinum in ethanol (70 ml) and THF (30 ml) for 1 h, followed by filtration and removal of solvents produced a brown gum. Flash chromatography over silica using ethyl acetate–methanol solvent and gradient elution produced firstly the *tricyclic dione* **4** (126 mg, 18%), as a semi-crystalline solid, λ_{max}/nm(EtOH) 278, 373 and 445; ν_{max}/cm^{-1}(film) 3620 and 1700; δ_H(CF_3CO_2D; 300 MHz) 4.16 (3 H, s, OCH_3), 4.26 (3 H, s, OCH_3), 7.44 (1 H, s, 5-H), 8.48 (1 H, d, *J* 6 Hz, 4-H) and 8.66 (1 H, d, *J* 6 Hz, 3-H); *m/z* (EI) 258 ($M^{\cdot+}$, 100%), 230 (65), 215 (57), 187 (71) and 144 (28) (Found: 258.0640. $C_{13}H_{10}N_2O_4$ requires 258.0640).

Secondly *aminoglyoxylate* **3p** as a brown oil (20 mg, 2%), λ_{max}/nm(EtOH) 253sh, 265sh, 293, 348, 420sh; ν_{max}/cm^{-1}(film) 3480, 1740 and 1690; δ_H($CDCl_3$) 1.44 (3 H, t, *J* 6 Hz, OCH_2CH_3), 3.96 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 4.46 (2 H, br s, NH_2), 4.53 (2 H, q, *J* 6 Hz, OCH_2CH_3), 7.8 (1 H, br s, 4-H), 8.22 (1 H, s, 5-H) and 8.56 (1 H, br s, 3-H); *m/z* (EI) 304 ($M^{\cdot+}$, 67%), 231 (34), 204 (57), 203 (100), 188 (43) and 173 (41) (Found: 304.1056. $C_{15}H_{16}N_2O_5$ requires 304.1059).

6,7-*Dimethoxyisoquinoline*-1-*carbaldehyde* **3q**.—Isoquinoline **3a** (2.0 g) and selenium dioxide (1.2 g) were heated together in refluxing dioxane (100 ml) for 2 h. The cooled, filtered (Celite) reaction mixture was evaporated under reduced pressure and the resulting crude material purified by recrystallisation from dichloromethane–light petroleum (b.p. 60–80 °C) to give pure aldehyde **3q** (1.49 g, 71%), m.p. 174–176 °C (lit.,[17] 176 °C), λ_{max}/nm(EtOH) 236, 262, 326 and 353 (log ε 4.58, 4.12, 3.59 and 3.54); ν_{max}/cm^{-1}(film) 1697; δ_H($CDCl_3$) 4.0 (3 H, s, OCH_3), 4.05 (3 H, s, OCH_3), 7.05 (1 H, s, 5-H), 7.65 (1 H, d, *J* 6 Hz, 4-H), 8.55 (1 H, d, *J* 6 Hz, 3-H), 8.65 (1 H, s, 8-H) and 10.25 (1 H, s, CHO); *m/z* (EI) 217 ($M^{\cdot+}$, 100%), 190 (25), 189 (98), 188 (46), 174 (34), 173 (13), 172 (17) and 159 (14).

6,7-*Dimethoxy*-8-*nitroisoquinoline*-1-*carbaldehyde* **3r** *and* 7-*Hydroxy*-6-*methoxy*-8-*nitroisoquinoline*-1-*carboxylic Acid* **5**.—To a stirred solution of the isoquinoline **3g** (3.38 g) in dry dioxane (300 ml), selenium dioxide (2.27 g) was added in one portion and the mixture heated at reflux for 2.5 h. The mixture was cooled to 50 °C, filtered (Celite) and the filtrate evaporated to provide crude material which was purified by flash chromatography over silica, eluting with a gradient of hexane and acetone, to provide the *aldehyde* **3r** (1.93 g, 54%), m.p. 203–205 °C, λ_{max}/nm(EtOH) 235, 295 and 308sh (log ε 4.34, 3.60 and 3.59); δ_H($CDCl_3$; 300 MHz) 4.09 (3 H, s, OCH_3), 4.11 (3 H, s, OCH_3), 7.30 (1 H, s, 5-H), 7.75 (1 H, d, *J* 5.5 Hz, 4-H), 8.66 (1 H, d, *J* 5.5 Hz, 3-H) and 10.12 (1 H, s, CHO); δ_C($CDCl_3$; 75 MHz) 56.64 (s, OCH_3), 63.05 (s, OCH_3), 108.49, 123.00, 142.58 (3 × aromatic CH), 112.97, 135.04, 140.81, 145.74, 150.07, 155.87 (6 × aromatic C) and 191.28 (CHO); *m/z* (EI) 262 ($M^{\cdot+}$, 39%), 230 (26), 217 (28), 216 (79), 189 (33), 188 (25), 187 (24), 176 (32), 172 (28), 161 (44), 160 (43), 158 (31), 148 (26), 145 (28), 144 (35), 130 (33), 128 (34), 117 (48), 116 (31), 115 (33), 104 (31), 102 (41), 91 (42), 89 (36), 77 (32), 76 (31), 75 (52), 71 (37), 63 (30), 51 (32) (Found: 262.0592. $C_{12}H_{10}N_2O_5$ requires 262.0590).

Then *acid* **5** (0.44 g, 12%), m.p. 140–185 °C (decomp.), ν_{max}(KBr) 3415, 3181, 1694; δ_H[$(CD_3)_2SO$; 300 MHz] 4.09 (3 H, s, OCH_3), 7.13 (1 H, s, 5-H), 7.86 (1 H, d, *J* 5.5 Hz, 4-H), 8.78 (1 H, d, *J* 5.5 Hz, 3-H), and 10.2 and 10.9 (br s and s, D_2O exchangeable, 2 × 1 H, HO and HO_2C); δ_C[$(CD_3)_2SO$; 75 MHz] 56.62 (OCH_3), 87.40, 120.37, 146.18 (3 × aromatic CH), 119.14, 119.38, 128.97, 131.56, 146.69 and 156.90 (6 × aromatic C) and 167.19 (CO_2H); *m/z* (EI) 217 ($M^{\cdot+}$ − NO_2, 0.03); *m/z* (FAB) 217 ($M^{\cdot+}$ − NO_2, 100%) (Found: C, 49.76; H, 3.00; N, 10.2. $C_{11}H_8N_2O_6$ requires C, 49.98; H, 3.05; N, 10.6%).

8,9-*Dimethoxy*-3-(6,7-*dimethoxy*-1-*isoquinolyl*)*imidazo*[5,1-a]*isoquinoline* **6a**.—The aldehyde **3q** (25 mg) was stirred with ammonium acetate (83 mg) in acetic acid (4 ml) at room temperature for 48 h. The precipitate which formed was filtered off, washed with acetic acid and water and dried to give the imidazoisoquinoline **6a** (21 mg, 88%) as yellow crystals, m.p. >260 °C, λ_{max}/nm(EtOH) 239, 254, 260 and 377 (log ε 4.29, 4.24, 4.26 and 3.80); δ_H($CDCl_3$; 300 MHz) 3.88 (6 H, s, 2 × OCH_3), 3.94 (6 H, s, 2 × OCH_3), 7.07 (1 H, d, *J* 7.5 Hz, 6-H), 7.36 (1 H, s, 1-H), 7.42 (1 H, s, ArH), 7.7 (1 H, d, *J* 6 Hz, 4′-H), 7.8 (1 H, s, ArH), 8.24 (1 H, s, ArH), 8.5 (1 H, d, *J* 6 Hz, 3′-H), 8.92 (1 H, s, ArH) and 9.19 (1 H, d, *J* 7.5 Hz, 5-H); *m/z* (CI) 416 (MH^+, 69%), 415 (18), 133 (15), 215 (41), 201 (13) and 1190 (33) (Found: 415.4530. $C_{24}H_{21}N_3O_4$ requires 415.4527).

8,9-*Dimethoxy*-3-(6,7-*dimethoxy*-8-*nitroisoquinolin*-1-*yl*)-10-*nitroimidazo*[5,1-a]*isoquinoline* **6b**.—The aldehyde **3r** (78 mg) was stirred in acetic acid (6 ml) with ammonium acetate (210 mg) at room temperature for 48 h. The precipitate was filtered off and dried to give the *imidazoisoquinoline* **6b** (72 mg, 96%) as yellow crystals, m.p. 210 °C, λ_{max}/nm(EtOH) 240, 253 and 366 (log ε 4.75, 4.7 and 4.05); δ_H($CDCl_3$; 300 MHz) 3.92 (6 H, 2 × OCH_3), 4.0 (3 H, s, OCH_3), 4.06 (3 H, s, OCH_3), 7.15 (1 H, s, 1-H), 7.15 (1 H, s, ArH), 7.17 (1 H, d, *J* 7.5 Hz, 6-H), 7.8 (1 H, s, ArH), 7.92 (1 H, s, ArH), 8.05 (1 H, d, *J* 6 Hz, 4′-H), 8.44 (1 H, d, *J* 7.5 Hz, 5-H) and 8.73 (1 H, d, *J* 6 Hz, 3′-H); *m/z* (CI) 506 (MH^+, 43%), 461 (19), 248 (11), 246 (10), 245 (13), 244 (11), 233 (15), 232 (11), 231 (50), 230 (37), 229 (11), 217 (21), 216 (16), 215 (50) and 205 (52) (Found: C, 56.5; H, 3.7; N, 13.8. $C_{24}H_{19}N_5O_8$ requires C, 57.0; H, 3.8; N, 13.9%).

2-(6,7-*Dimethoxy*-8-*nitro*-1-*isoquinolyl*)-1,3-*dinitropropane* **3u**.—To a stirred suspension of aluminium oxide (activated,

basic; 1 g) in nitromethane (3 ml) was added the aldehyde **3r** (51 mg) and the mixture stirred at reflux under nitrogen for 3.5 h. The alumina was filtered off, washed with acetone and methanol and the combined organic filtrates were evaporated to leave a residue which was purified by flash chromatography over silica, eluting with dichloromethane to provide the *trinitroisoquinoline* **3u** (37 mg, 51%), m.p. 153 °C, δ_H($CDCl_3$; 300 MHz) 4.05 (3 H, s, OCH_3), 4.08 (3 H, s, OCH_3), 4.56 [1H, p, *J* 6.6 Hz $CH(CH_2NO_2)_2$], 4.74, 4.76 (2 H, dd, *J* 14.3, 6.6 Hz, CH_2NO_2), 5.14, 5.16 (2 H, dd, *J* 14.3 and 6.6 Hz, CH_2NO_2), 7.25 (1 H, s, 5-H), 7.54 (1 H, d, *J* 5.5 Hz, 4-H) and 8.42 (1 H, d, *J* 5.5 Hz, 3-H); δ_C($CDCl_3$; 75 MHz) 38.50 [$CH(CH_2NO_2)_2$], 56.61 (OCH_3), 62.98 (OCH_3), 75.32 (CH_2NO_2), 77.25 (CH_2NO_2), 108.70, 120.30, 140.62, 114.04, 135.43, 140.62, 143.78, 155.14 (9 × Ar-C); *m/z* (EI) 366 ($M^{\cdot+}$, 80), 273 (100), 244 (64), 243 (45), 230 (30), 229 (31), 228 (45), 216 (42), 215 (32), 214 (34) and 200 (37) (Found: 366.0810. $C_{14}H_{14}N_4O_8$ requires 366.0812).

1-(6,7-*Dimethoxy*-8-*nitro*-1-*isoquinolyl*)-2-*nitroethanol* **3s**.—To a stirred suspension of aluminium oxide (activated, basic; 1.86 g) in nitromethane (65 ml), the aldehyde **3r** (0.60 g) was added within 2 min; stirring was then continued for 3.5 h. The aluminium oxide was filtered off, washed with acetone and methanol and the combined organic solutions were evaporated to produce crude alcohol **3s** (0.65 g, 84%) which was pure enough to be used directly for conversion into the nitroalkene **3t**. A small sample of *alcohol* **3s** was purified by chromatography over silica, eluting with hexane–acetone in gradient, m.p. 158–160 °C, λ_{max}/nm(EtOH) 235, 294, 310 and 325; δ_H($CDCl_3$; 300 MHz) 1.75 (1 H, br s, OH), 4.04 (3 H, s, OCH_3), 4.10 (3 H, s, OCH_3), 4.50, 4.53 (1 H, dd, *J* 13.1 and 8.3 Hz, $CHNO_2$), 4.73, 4.74 (1 H, dd, *J* 13.1 and 2.8 Hz, $CHNO_2$), 5.64, 5.65 [1 H, dd, *J* 8.3, 2.8 Hz, $CH_2CH(OH)$], 7.30 (1 H, s, 5-H), 7.65 (1 H, d, *J* 5.6 Hz, 4-H) and 8.49 (1 H, d, *J* 5.6 Hz, 3-H); δ_C ($CDCl_3$; 75 MHz) 56.64 (OCH_3), 62.91 (OCH_3), 67.21 (CH_2NO_2), 81.25 (CHOH), 108.67, 121.02, 141.17 (3 × aromatic CH), 112.45, 135.32, 141.17, 143.99, 151.83, 155.44 (6 × aromatic C); *m/z* (EI) 323 ($M^{\cdot+}$, 35), 263 (100), 231 (31), 217 (34), 216 (66), 189 (44), 160 (30), 117 (33), 58 (30) and 43 (64) (Found: 323.0749. $C_{13}H_{13}N_3O_7$ requires 323.0753).

After chromatography, in addition to the alcohol **3s**, a small amount of original nitromethylisoquinoline **3g** was obtained, **3s**:**3g** (84:16).

1-(6,7-*Dimethoxy*-8-*nitro*-1-*isoquinolyl*)-2-*nitroethene* **3t**.—In an apparatus arranged for azeotropic removal of water, aluminium oxide (activated, basic, 1.15 g) and the alcohol **3s** (364 mg) were heated in benzene (60 ml), with continuous distillation for 1 h. Filtration, and evaporation of the filtrate and methanol washings of the alumina, produced a mixture of compounds (180 mg) which were separated by chromatography over silica, eluting with dichloromethane, to give, in order of elution, the trinitroisoquinoline **3u** (22 mg), the *nitroalkene* **3t** (97 mg, 36%), the aldehyde **3r** (43 mg) and the isoquinoline **3g** (39 mg) (present in starting alcohol, see above). The nitroalkene **3t** had m.p. 188–190 °C, δ_H($CDCl_3$; 300 MHz) 4.06 (3 H, s, OCH_3), 4.09 (3 H, s, OCH_3), 7.26 (1 H, s, 5-H), 7.67 (1 H, d, *J* 5.5 Hz, 4-H), 7.93 (1 H, d, *J* 12.6 Hz, $CH{=}CHNO_2$), 8.14 (1 H, d, *J* 12.6 Hz, $CH{=}CHNO_2$) and 8.57 (1 H, d, *J* 5.5 Hz, 3-H); δ_C($CDCl_3$; 75 MHz) 57.03 (OCH_3), 63.33 (OCH_3), 108.52, 115.17, 122.12, 133.25, 135.34, 143.68, 143.90, 144.01, 144.14, 145.11, 155.69 (9 × Ar–C and C=C); *m/z* (EI) 305 ($M^{\cdot+}$, 4%), 216 (50), 28 (100) (Found: 305.0647. $C_{13}H_{11}N_3O_6$ requires 305.0648).

8,9-*Dimethoxy*-1H-*benzo*[d,e][1,6]*naphthyridine* (*Aaptamine*) **1a** *Hydrochloride*.—To a stirred solution of the nitroalkene **3t** (6 mg) in acetic acid (0.5 ml) and ethanol (0.5 ml) was added iron powder (28 mg) in one portion. The resulting suspension was stirred under argon for 2 h at room temperature and then for 0.75 h at 80–90 °C. After addition of water and basification with solid sodium hydrogen carbonate, organic material was extracted with chloroform, all operations being conducted under argon. The extract was concentrated under reduced pressure and the concentrated solution applied to a flash column of neutral alumina, eluting with a gradient of chloroform and methanol. The eluate was saturated with hydrogen chloride, and the solvent and excess hydrogen chloride were evaporated leaving aaptamine hydrochloride (5 mg, 89%), m.p. 108–112 °C (lit.,[1] 110–113 °C), with UV–VIS, IR and NMR properties identical with those reported.[1]

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